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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,295	10/15/2001	Avi Ashkenazi	GNE.2630P1C11	6495

35489 7590 05/31/2006

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ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/31/2006

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/978,295
Filing Date: October 15, 2001
Appellant(s): ASHKENAZI ET AL.

Barrie D. Greene
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 24 March 2006 appealing from the Office action mailed 29 August 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

While there are no related cases under appeal, interference, or judicial proceedings, there are two related cases. 09/999,833 is a patented case claiming nucleic acids. 09/978,194 is a case under final rejection claiming polypeptides that bind the antibodies claimed in the instant application. '194 has similar issue to those discussed herein.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. However, an after final response received 07 December 2005 (containing only arguments but no claim amendments) was entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct. Of course, the examiner disagrees with any assertion of the patentability of the claimed invention for reasons discussed herein.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct. Appellants' attention is directed to an obvious typographical error in claim 62, present in both the official copy of the claims (received 28 October 2005) and the Brief's claims appendix, wherein claim 62 should depend from claim 58 instead of from canceled claim 28. Note that this typographical error was not present in a previous official claim set received 29 April 2004. This error can be addressed after the decision by the Board of Appeals and Interferences.

(8) Evidence Relied Upon

Pennica et al., 1998, PNAS USA 95:14717-14722.

Konopka et al., Proc. Natl. Acad. Sci. (1986) 83:4049-4052.

Chen et al., 2002, Molecular and Cellular Proteomics 1:304-313.

Hu et al., 2003, Journal of Proteome Research 2:405-412.

LaBaer, 2003, Nature Biotechnology 21:976-977.

Haynes et al., 1998, Electrophoresis 19:1862-1871.

Gygi et al., 1999, Mol. Cell. Biol. 19:1720-1730.

Lian et al., 2001, Blood 98:513-524.

Fessler et al., 2002, J. Biol. Chem. 277:31291-31302.

Hanna et al., 1999, Pathology Associates Medical Laboratories.

Greenbaum et al., 2003, Genome Biology 4 :117.1-117.8.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 58-62 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to an antibody that specifically binds to the polypeptide of SEQ ID NO: 132. Claims are also presented to various forms of antibody, including monoclonal, humanized, fragment, and labeled antibodies. The utility and enablement of the claimed antibodies depends on whether or not the polypeptide of SEQ ID NO: 132 has utility and is enabled. The specification discloses the polypeptide of SEQ ID NO: 132, also known as PRO351. Appellants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed antibodies. See Appeal Brief, p. 4, beginning of arguments. (It is noted that the specification asserts several other utilities for the claimed polypeptides [and, by extension, their antibodies], all of which have been found to be non-specific and/or insubstantial. For discussion of these utilities, see Office Action mailed 04 February 2004. However, these asserted utilities will not be re-addressed here due to Appellants' indication that they are relying upon the gene amplification assay for utility and enablement.)

At pages 331-346, Example 114 discloses a gene amplification assay in which genomic DNA encoding PRO351 had a ΔCt value of at least 1.0 for ten out of nineteen lung tumor samples. Example 114 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the

polypeptides (and their antibodies) are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 331, lines 25-27). Genomic DNA encoding PRO351 was not amplified in any of the seventeen colon tumor samples. At page 337, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 340, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 341-345 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

While these data support utility and enablement of PRO351 *genomic DNA* for use in lung tumor diagnosis, the data have no bearing on the utility of PRO351 *polypeptides and antibodies*. In order for PRO351 polypeptides to be overexpressed in lung tumors, amplified genomic DNA would have to correlate with increased mRNA levels, which in turn would have to correlate with increased polypeptide levels. No data regarding PRO351 mRNA or PRO351 polypeptide levels in colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between mRNA levels and polypeptide levels. Regarding the correlation between genomic DNA

amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

Moreover, even if increased mRNA levels could be established for PRO351, it does not follow that PRO351 polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean mRNA expression level between

breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying mRNA changes of 5-fold or less in tumors compared to normal, there was no evidence of a correlation between altered mRNA expression and a known role in the disease. However, among genes with a 10-fold or more change in mRNA expression level, there was a strong and significant correlation between mRNA expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels

> varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Finally, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) caution against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not

be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, the literature shows that those skilled in the art would not assume that increased mRNA levels are predictive of increased protein levels.

Therefore, data pertaining to PRO351 genomic DNA do not indicate anything significant regarding the claimed antibodies that bind PRO351 polypeptides. The data do not support the specification's assertion that PRO351 polypeptides and their antibodies can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO351 polypeptides are overexpressed in any cancer to the extent that they or their antibodies could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO351 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO351 **polypeptides or antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689

(Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 58-62 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

In general, Appellants' organization of arguments will be followed.

Appellants' Summary of Arguments

Issue I: Utility

At p. 4 of the Brief, Appellants argue that the patentable utility of PRO351 antibodies is based on the gene amplification data for the gene encoding the PRO351 polypeptide. Appellants state that the specification shows significant amplification of the gene encoding PRO351 in ten different lung tumors. Appellants refer to the declaration of Dr. Goddard (submitted under 37 C.F.R. § 1.132 on 29 April 2004) as explaining that a gene that is amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful for the diagnosis of cancer, for

monitoring cancer development, and/or for measuring the efficacy of cancer therapy. Appellants urge that such a gene is useful as a marker for the diagnosis of lung cancer. This has been fully considered but is not found to be persuasive, as it does not address the utility of the claimed subject matter, i.e., PRO351 *antibodies*. It is maintained that the gene amplification assay does not provide a patentable utility for polypeptides or antibodies because amplified genomic DNA is not predictive of increased mRNA or polypeptide levels, for reasons discussed herein. For example, the art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Greenbaum et al.). Since the instant claims are directed to antibodies that bind polypeptides, this is a major concern. The Goddard declaration was not found to be sufficient to overcome the rejection; however, the Goddard declaration will be addressed at length later in this answer.

From p. 4 to p. 5 of the Brief, Appellants argue that the examiner has characterized the amplification of PRO351 as very small without evidence. Appellants argue that the control used in the specification is acceptable since peer reviewed papers also use it as a negative control. Finally, Appellants take issue with the Hittelman et al. reference. This has been fully considered but is not found to be persuasive. Due to the fact that the PRO351 nucleic acids have been allowed in related application 09/999,833, the examiner will no longer maintain issues regarding the significance of the gene amplification itself. Rather, the reason why the instant claimed antibodies have been rejected for lack of utility and enablement hinges on the evidence

of record that gene amplification does not correlate with increased mRNA expression, and increased mRNA expression does not correlate with increased polypeptide levels.

At p. 5, Appellants argue that the examiner has applied an improper legal standard requiring a necessary correlation or accurate prediction. Appellants urge that the rejection and references cited in support thereof fail to establish that it is more likely than not that the skilled artisan would doubt the truth of the statement of utility. Appellants argue that ample evidence has been provided to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide is also expressed at an elevated level. Appellants refer to Orntoft et al., Hyman et al. and Pollack et al. as teaching that, in general, gene amplification increases mRNA expression. Appellants point to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on 28 June 2004) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Appellants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellants assert that the research community believes that the information obtained from these chips is useful. Finally, Appellants conclude that there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO351 conveys utility to the claimed PRO351 polypeptides and their antibodies. This has been fully considered but is not found to be persuasive. Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., and LaBaer all speak to large sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in

this answer. Further research would be needed to determine PRO351 polypeptide levels in cancers showing gene amplification of PRO351 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO351 polypeptides as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes, but not polypeptides. Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

At p. 6 of the Brief, Appellants urge that, while there may be exceptions, the central dogma of molecular biology is that there is a general correlation between DNA, mRNA, and protein levels. Appellants again refer to Orntoft et al., Hyman et al., Pollack et al., and the Polakis declaration. Appellants urge that even if there were no correlation between gene amplification and mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer still has a patentable utility in that such yields in more accurate tumor classification, relying upon the declaration by Dr. Ashkenzi (submitted under 37 C.F.R. § 1.132 on 18 June 2004) and the Hanna et al. reference. This has been fully considered but is not found to be persuasive. Haynes et

al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., and LaBaer all speak to large sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in this answer. Regarding the Ashkenazi declaration and the Hanna et al. reference, the specification does not disclose that the PRO351 polypeptide levels increase **or** stay the same. Further research would be needed to determine PRO351 polypeptide levels in cancers showing gene amplification of PRO351 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO351 polypeptides as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides. The Ashkenazi declaration (submitted under 37 C.F.R. § 1.132 on 24 October 2003) will be addressed in detail later in this answer. The Hanna et al. reference actually supports the rejection, since Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Issue II: Enablement

At p. 7, Appellants argue that PRO351 polypeptide and antibodies have utility in the diagnosis of cancer and thus the skilled artisan would know how to use the claimed subject matter without undue experimentation. This has been fully considered but is not

found to be persuasive because the claimed PRO351 antibodies do not have utility as discussed herein.

Appellants' Response to Rejections

ISSUE I: Appellants argue that claims 58-62 satisfy the utility requirement of 35 U.S.C. § 101

A. The legal standard for utility

At pp. 7-10 of the Brief, Appellants review the legal standard for utility, with which the examiner takes no issue.

B. Appellants argue that the data and documentary evidence support a patentable utility

At p. 10 of the Brief, Appellants argue that the data in Example 114 describes results of a gene amplification assay. Appellants assert that gene amplification is an essential mechanism for oncogene activation. Appellants review how the assay was performed, and reports that the gene encoding PRO351 was significantly amplified (2.03-fold to 2.75-fold) in ten lung tumors. This has been fully considered but is not found to be persuasive. The data pertaining to gene amplification do not convey utility to the claimed antibodies that bind PRO351 polypeptide, since amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al.).

At p. 11 of the Brief, Appellants argue that gene amplification occurs in most solid

tumors and is associated with poor prognosis. This has been fully considered but is not found to be persuasive. Gene amplification may provide relevant information for use of a **gene probe** in diagnosis or prognosis of cancer. However, it has no bearing on the use of polypeptides or antibodies in cancer diagnosis or prognosis since gene amplification does not correlate with increased mRNA or polypeptide levels.

Also at p. 11 of he Brief, Appellants refer to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 20 May 2005. Appellants quote from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellants conclude that one skilled in the art would consider the amplification of the gene encoding PRO351 in ten lung tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not the amplification of the gene encoding PRO351 in ten lung tumors is significant and credible. Credibility has never been questioned. However, the significance can be

questioned relative to the *claimed* subject matter, namely, antibodies that bind PRO351 *polypeptide.* Hu et al. and Chen et al. speak to the strength of the opposing evidence, as do Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al., discussed in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed in the rejection above. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO351 gene has *not* been associated with tumor *formation* or the *development* of cancer, nor has it been shown to be predictive of such. Similarly, the PRO351 gene has *not* been shown to be useful to track the *efficacy of cancer therapy*. The specification merely demonstrates that the PRO351 genomic DNA is amplified in some lung cancers compared to normal DNA from blood. No mutation or translocation of PRO351 has been associated with any type of cancer versus normal tissue. It is not known whether PRO351 mRNA or polypeptide, as recited in the claims, are elevated in any cancerous tissue. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO351 is amplified in a variety of samples and invites the artisan to determine the significance of this increase relative to the claimed subject matter. It remains that, as evidenced by the references of record, the issue is simply not

predictable, and the specification presents a mere invitation to experiment. Based on consideration of the preponderance of the totality of the evidence as a whole, the rejection is proper.

From the bottom of p. 11 to the middle of p. 16 of the Brief, Appellants provide arguments regarding whether or not the gene amplification was small or significant, whether or not the control was proper, and the significance of aneuploidy. Upon further consideration, and in view of the allowance of the nucleic acid claims in related application 09/999,833, these issues are no longer deemed relevant to the utility and enablement of the instantly claimed antibodies. Specifically, the gene amplification assay was found to support utility and enablement for *specific* nucleic acids (although no claims to *generic* nucleic acids encoding the PRO351 polypeptide were allowed). The important issue regarding utility and enablement of the instantly claimed antibodies is whether or not results of the gene amplification assay are relevant to polypeptides (and their antibodies). It is maintained that gene amplification is not predictive of increased mRNA levels which, in turn, are not predictive of increased polypeptide levels. Therefore, the rejections are maintained.

C. Appellants urge that a *prima facie* case of lack of enablement has not been established

At pp. 16-17 of the Brief, Appellants argue that it is not a legal requirement to establish that gene amplification necessarily results in increased expression at the mRNA and polypeptide levels, or that polypeptide levels be accurately predicted. Appellants urge that the proper legal standard the examiner must establish is that it is

more likely than not that the skilled artisan would doubt the truth of the statement of utility. This has been fully considered but is not found to be persuasive. The rejection is based on the preponderance of the totality of the evidence that it is more likely than not that gene amplification does not correlate with increased mRNA levels and increased polypeptide levels. In view of this evidence, the asserted utility that PRO351 polypeptides and their antibodies can be used in cancer diagnostics is not substantial in that further experimentation would be required to reasonably confirm the real-world use of the claimed antibodies. Credibility of the assertion of utility has not been questioned since it is certainly possible that PRO351 polypeptides are overexpressed in lung tumors.

1. Pennica et al. and Konopka et al.

At pp. 17-18 of the Brief, Appellants take issue with the Pennica et al. and Konopka et al. references relied upon by the examiner. Specifically, Appellants characterize Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Appellants point out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Appellants characterize Konopka et al. as supporting Appellant's position, and being limited to the abl gene, and not speaking to genes in general. Appellants conclude that the examiner must show evidence that it is more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene

amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. The evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al.), and (3) no evidence has been brought forth regarding levels of PRO351 mRNA levels or PRO351 polypeptide levels in cancerous tissue.

2. Hu et al. and LaBaer

At pp. 19-20 of the Brief, Appellants criticize the Hu et al. reference. Specifically, Appellants criticize Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Appellants characterize Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Appellants criticize the types of statistical tests performed by Hu et al. Appellants conclude that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed antibodies that bind PRO351 polypeptide is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the

second presumption is incorrect when designating proteins (or their antibodies) as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO351 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO351 protein or antibodies that bind it can be used as a cancer diagnostic. It is noted that Hu et al. appeared in a peer-reviewed journal, and thus the statistical analysis reported therein was found to be accepted by those in the art. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO351 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA

expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO351 mRNA or polypeptide is overexpressed in cancer, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Appellants' criticism of Hu et al.'s statistical analysis, Appellant is holding Hu et al. to a higher standard than their own specification, which does not provide *any* statistical analysis such as reproducibility, standard error rates, etc. Regarding Appellants' criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At p. 21 of the Brief, Appellants argue that statistical analysis is important for Hu et al. since they are looking at relevance of published data. Appellants urge that the specification reports comparison of normal tissue and lung tumor, showing greater than 2-fold amplification. This has been fully considered but is not found to be persuasive. Statistical analysis is important in any scientific inquiry.

At pp. 21-22 of the Brief, Appellants urge that LaBaer is an unreviewed letter to the editor and provides no further evidence than the Hu et al. publication. This has been fully considered but is not found to be persuasive since LaBaer is the published opinion of an expert in the field. LaBaer states that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples.

3. Chen et al.

At p. 22 of the Brief, Appellants argue that Chen et al. is deficient for using 2D gels, which do not detect low abundance proteins which are likely to be significant as cancer markers. This has been fully considered but is not found to be persuasive. While 2D gels might exclude low abundance proteins, their use is valid for detectable proteins. Chen et al. focused on those mRNA which encoded proteins that were detectable on 2D gel (p. 308, col. 2). The method was sensitive enough to determine that proteins having different isoforms also often had different protein/mRNA correlation coefficients (p. 309, paragraph bridging col. 1-2). It was concluded that absolute protein level did not influence the correlation with mRNA (p. 310, col. 1). Additionally, the correlation coefficient was not arbitrarily chosen, but was based on detailed statistical analysis that resulted in those values above the assigned correlation coefficient to be considered significant if the designated difference was above the threshold (see paragraph bridging pages 307-308). The results of Chen lead to the conclusion that post-translation modifications are likely to affect the correspondence (or lack thereof) of

mRNA to protein levels (see Discussion). Further it was shown (p. 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with their encoded proteins. 2D-PAGE is a common method of protein analysis, when the limitations are taken into account, as with Chen et al., the results are noteworthy.

At pp. 22-23 of the Brief, Appellants argue that Chen et al. looked at many tumor samples 976) and a much smaller number of normal samples (9). Appellants characterize the tumor samples as being diverse. Appellants argue that the numerical analysis was flawed. Appellants urge that no attempt was made to compare expression levels in normal versus tumor samples, and thus the results of Chen et al. are not applicable to the instant application. Appellants argue that the analysis of Chen et al. is not correct, and that of the 66 genes with no isoforms, 40/66 had a positive correlation between mRNA and protein expression (Table 1). In Table II, which showed 30 genes with multiple isoforms, 22/30 showed a positive correlation between one isoform of each gene. No genes showed a negative isoform correlation. This has been fully considered but is not found to be persuasive. On page 309, first full sentence, Chen et al. state, "Among the 69 genes for which only a single protein spot was known (Table I), nine

genes (9/69, 13%) were observed to show a statistically significant relationship between protein and mRNA abundance..." Table I considered significance at $p<0.05$. Chen et al. is relied upon for teaching that assumptions cannot be made concerning mRNA/protein correlation with a reasonably certainty. The paper clearly answered the question posed: Does mRNA expression correlate with protein expression in lung tumor samples? The answer was 'no' in a majority of cases. This result directly supports the Examiner's finding that the art does not sustain a reasonable expectation that for any particular mRNA expressed in tumor, the amount of protein and encoding mRNA will correlate. Finally, Chen et al. appeared in a respected, peer-reviewed journal, and thus the implication that Chen et al. made faulty calculations is not well-founded.

4. Haynes et al. and Gygi et al.

At pp. 23-24 of the Brief, Appellants argue that Haynes et al. never indicate that the correlation between mRNA and protein does not exist, rather, Haynes et al. is characterized as stating that protein levels cannot accurately be predicted from mRNA levels. Appellants admit that such is expected since there are many factors that determine translation efficiency for a given transcript or half-life of the encoded protein. Appellants argue that Haynes et al. do not state that a change in level of mRNA is not predictive of a change in protein level. Appellants also urge that Haynes et al. support Appellants' position when they state that there was a general trend between protein expression and transcript levels. Appellants reiterate that accurate prediction is not the legal standard. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from

the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general. Just because Haynes et al. are silent with respect to other issues does not mean that Haynes et al. agrees with Appellants' position. Finally, Appellants admit that protein levels cannot accurately be predicted from mRNA levels since there are many factors that determine translation efficiency for a given transcript or half-life of the encoded protein. Once one accepts this, one must also accept that these factors can also change in tumor cells such that an increase in mRNA may not correlate with increased protein levels (due to increased degradation levels, for example). In fact, those looking at mRNA levels and protein levels in lung tumors found a lack of correlation. See Chen et al.

At pp. 25-26 of the Brief, Appellants argue that Gygi et al. failed to look at changes in mRNA levels for a single gene, and thus are limited to findings relevant to constant levels of mRNA and protein across different genes. Appellants further argue that Gygi et al. only state that mRNA levels cannot accurately predict protein levels, not that there is a lack of correlation between mRNA levels and protein levels. Appellants urge that Gygi et al. report a general trend of correlation between transcript and protein levels. This has been fully considered but is not found to be persuasive. Gygi et al. clearly looked at transcript levels and protein levels for particular genes. They state that, "the correlation between mRNA and protein levels was insufficient to predict

protein expression levels from quantitative mRNA data. Indeed, **for some genes**, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with **respective** mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (emphasis added).

5. Lian et al.

At pp. 26-28, Appellants take issue with the Lian et al. reference. Appellants argue that the Lian et al. publication is limited to differentiating myeloid cells and does not teach anything regarding a lack of correlation between mRNA levels and protein levels in general. Appellants also find fault with Lian et al. for using a relatively insensitive assay. Finally, Appellants argue that Lian et al. did not look at change in mRNA levels and whether or not they predicted changes in protein levels. This has been fully considered but is not found to be persuasive. Lian et al. show a lack of correlation between mRNA levels and polypeptide levels in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels.") This is directly on point for the instant issue. Furthermore, Appellants again hold the reference to a higher standard than their own specification. Lian et al. used an art-accepted method to measure polypeptide levels whereas the instant specification and evidence of

record do not report using any method to detect PRO351 polypeptide levels.

6. Fessler et al.

At pp. 28-30, Appellants criticize the Fessler et al. reference. Appellants argue that Fessler et al. supports the specification's implicit assertion that a change in mRNA levels is predictive of a similar change in protein levels, pointing to Table VIII. This has been fully considered but is not found to be persuasive because Fessler et al. found a "[p]oor concordance between mRNA transcript and protein expression **changes**" in human cells (emphasis added, p. 31291, abstract), which is directly on point regarding the instant issue. It is noted that Fessler et al. appeared in a peer-reviewed publication.

7. Greenbaum et al.

At pp. 30-31, Appellants take issue with the Greenbaum et al. reference. Appellants urge that Greenbaum et al. is limited to yeast cells, and do not examine change between cancer and normal cells. Appellants quote from Greenbaum et al. that a high degree of correlation occurs for particular ORFs (open reading frames) that have higher than average levels of ribosomal association. This has been fully considered but is not found to be persuasive. There is no evidence of record that PRO351 corresponds to one of these type of ORFs. The main thrust of Greenbaum et al. is that there is a lack of correlation between mRNA and protein, in yeast, **and** eukaryotic cells. As set forth in the rejection, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) caution against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between

mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, **most notably in human cancers** and yeast cells. And, for the most part, they have reported only **minimal and/or limited correlations**. (emphasis added)

D. Appellants argue that it is "more likely than not" for amplified genes to have increased mRNA and protein levels

At pp. 31-32 of the Brief, Appellants argue that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer it is more likely than not that the encoded protein is overexpressed. Appellants point to Orntoft et al., Hyman et al., and Pollack et al. in support thereof. Specifically, Appellants characterize Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellants characterize Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellants characterize Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated

with a corresponding 1.5-fold increase in mRNA levels. Appellants conclude that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO351 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in colon cancer.

At pp. 32-33 of the Brief, Appellants refer to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 28 July 2004. Appellants

characterize the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellants conclude that all of the submitted evidence supports Appellants' position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO351 (i.e., data regarding amplification of PRO351 genomic DNA), and does not disclose any information regarding PRO351 mRNA levels. Furthermore, there is strong opposing evidence showing that gene

amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., and Fessler et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased mRNA and polypeptide levels? Were they of the same levels seen with PRO351?

At p. 33 of the Brief, Appellants note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellants conclude that the research community believes that the information obtained from the chips is useful (i.e., that it is more likely than not that the results are informative of protein levels). This has been fully considered but is not found to be persuasive. Evidence of commercial success has no bearing on the issue of utility. The research community could just as easily be interested in the gene chips as a way of providing preliminary results, which would then be followed up with actual testing of protein levels.

At pp. 33-38 of the Brief, Appellants take issue with the examiner's treatment of Orntoft et al., Hyman et al., and Pollack et al. Appellants reiterate their reliance on Orntoft et al., Hyman et al., and Pollack et al. At pp. 38-41, Appellants again refer to the Polakis declaration, and take issue with the examiner's treatment thereof. Appellants stress that the Polakis declaration was based on factual findings, and that the examiner must accept the opinion of an expert. Appellants urge that the examiner's reliance on Pennica et al., Konopka et al., Hu et al., Haynes et al., Lian et al., Fessler et al., Chen et al., LaBaer, Gygi et al., and Greenbaum et al. as opposing evidence is insufficient, reiterating their criticisms of the references. These arguments have been fully considered but are not found to be persuasive for the reasons set forth above in the discussion of these references and the declaration. The rejection is maintained based upon a fresh consideration of the totality of the evidence. The preponderance of the totality of the evidence supports the rejection.

E. Appellants urge that, even is a *prima facie* case of lack of utility has been established, it should be withdrawn based on consideration of the totality of the evidence

From p. 41 to p. 42 of the Brief, Appellants point to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 29 April 2004, as establishing that, even if the protein were not overexpressed, the simultaneous testing of gene amplification and gene product overexpression would enable more accurate tumor classification and thus the protein has utility whether or no I is overexpressed in cancer. Appellants conclude that such a situation would allow for better tumor classification and better

determination of suitable therapy. Appellants argue that absence of overexpression is crucial information for a clinician, because it indicates that the patient should not be treated with agents that target that gene product. Appellants argue that this saves money and benefits the patients who can avoid exposure to the side effects associated with such agent. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO351 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO351 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO351. For example, neither the specification nor the prior art discloses an agent that targets PRO351 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At p. 42 of the Brief, Appellants argue that the opinion of Dr. Ashkenazi is supported by the Hanna and Mornin reference. Appellants urge that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Appellants argue that

the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna and Mornin support the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with protein over-expression, and thus the level of protein expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, the asserted utility is not substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna and Mornin, Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO351 polypeptide. Identifying a drug specific for PRO351 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO351 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

At p. 42 of the Brief, Appellants argue that the gene encoding PRO351 polypeptide is amplified in at least ten lung tumor samples. Appellants characterize the PRO351 gene as a tumor associated gene. Appellants urge that, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Appellants argue that one

skilled in the art would expect the PRO351 polypeptide to be overexpressed in lung tumor tissues based on the PRO351 gene amplification data. This has been fully considered but is not found to be persuasive. In order for PRO351 polypeptides to be overexpressed in lung tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that there is no correlation between genomic DNA amplification and increased mRNA levels for two out of three WISP genes. Regarding correlation between amplified genomic DNA and elevated polypeptide levels, Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Regarding whether or not elevated mRNA levels are generally predictive of elevated polypeptide levels in diseased tissues, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of

Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977). The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) reached similar conclusions on their study of over 150 polypeptides. Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514,

top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Finally, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear

picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

At p. 43 of the Brief, Appellants argue that, even if the protein is not overexpressed, it would be useful in determining the course of treatment, again referring to the Ashkenazi declaration and the Hanna et al. reference. Appellants urge that the examiner's concern regarding the need for further testing of the PRO351 protein is unfounded, as such testing is really for further characterization of the tumors in which the PRO351 gene is amplified. Appellants argue that the PRO351 polypeptide is useful in tumor categorization. This has been fully considered but is not found to be persuasive. The specification asserts that elevated PRO351 polypeptide levels in a lung sample is indicative of lung cancer. However, according to Appellants' arguments, lack of overexpression may also correlate with a diagnosis of cancer. This leaves the skilled artisan at a loss as to what the utility of the PRO351 polypeptide or its antibodies is. The specification does not disclose whether or not PRO351 polypeptide is overexpressed in tumor tissue. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO351 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO351 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor

overexpresses PRO351. For example, neither the specification nor the prior art discloses an agent that targets PRO351 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. This is not merely further characterizing a tumor, but further research aimed at how PRO351 polypeptide or antibodies are useful.

In conclusion, data pertaining to PRO351 genomic DNA do not indicate anything significant regarding the claimed PRO351 polypeptides or antibodies. The data do not support the specification's assertion that PRO351 antibodies can be used as a cancer diagnostic agent or as a therapeutic drug development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO351 polypeptide is overexpressed in any cancer to the extent that it or its antibodies could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO351 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO351 **polypeptides or antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1206), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove

> to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Further, it is noted that M.P.E.P. § 2107 i states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO351 polypeptides and their antibodies are useful as diagnostic markers for cancer or as therapeutic targets for cancer drugs is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO351 polypeptide to be useful as a cancer diagnostic or therapeutic target, there must be a detectable change in the amount or form of PRO351 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al., Greenbaum et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO351 polypeptides or antibodies can be used as a cancer diagnostic agent.

ISSUE II: Appellants argue that claims 58-62 satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph

At pp. 43-44 of the Brief, Appellants argue that PRO351 polypeptide has utility in the diagnosis of cancer. Appellants urge that, based on such a utility, the skilled artisan would know exactly how to use antibodies that bind PRO351 polypeptide without undue experimentation. This has been fully considered but is not found to be persuasive. As discussed above, the preponderance of the totality of the evidence indicates that the claims PRO351 antibodies lack utility. Furthermore, the courts in Rasmusson v SmithKline, 75 USPQ2d 1297 (CAFC 2005) found that, "[i]f mere plausibility were the test of enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirements that the inventor enable an invention rather than merely proposing an unproved hypothesis." (bottom of p.1301).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Argument

Appellants have not requested an oral hearing as of the date of this Examiner's Answer. However, if Appellants request an oral hearing, the examiner wishes to have the opportunity to present oral arguments.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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